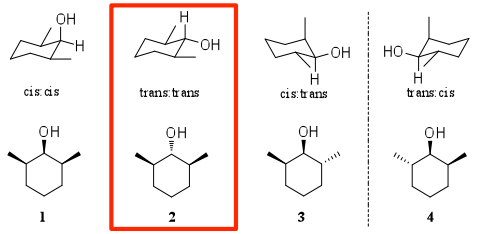
Synthesis and Purification of 2,6-dimethylcyclohexanol for Application as a General Anesthetic

K. Smith, M.J. Kim, R. Sinha, and K. M. Shea*

Smith College, Chemistry Department, Northampton, MA 01063

kshea@smith.edu

Project Goal



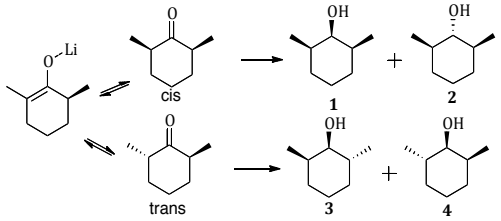
Synthesize *trans,trans*-2,6-dimethylcyclohexanol using selective methods

Past Work

- The initial goal of this project was separating the stereoisomers for testing by the Hall lab of the individual stereoisomers.
- These separations, based on chromatographic techniques, were completed last year by Alex Page for her honors thesis.
- These separations, after many attempts at optimization, failed to separate the stereoisomers, except for separation of the *cis,cis* isomer in large quantities.
- Preliminary testing by the Hall lab showed the *trans,trans* isomer to be most potent of the isomers.
- As a result, this current project switched to synthesizing *trans,trans*-2,6-dimethylcyclohexanol.

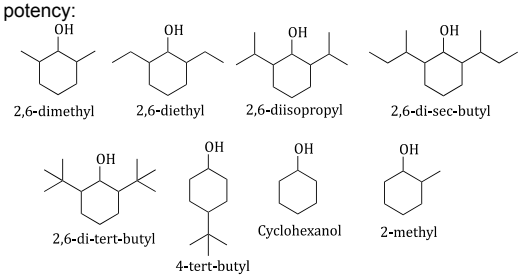
Isomerization

Both reduction and isomerization can occur in these reactions dictating the stereochemical outcome..



Background

- Propofol, a common anesthetic, has been shown to act on the $GABA_A$ receptor.
- Like many anesthetics, mysteries still remain
- about propofol's action.
- Push to develop new anesthetics to:
  - uncover anesthetics with fewer side effects.
  - allow for more testing to understand the anesthetic action and mechanisms of action for anesthetics in general.
- Based on previous study of propofol analogs, Adam Hall's neuroscience lab investigated various cyclohexanols due to their structure similarity to propofol, cyclohexanols being fully hydrogenated propofol analogs.
- A few of the cyclohexanol derivatives that showed anesthetic potency:



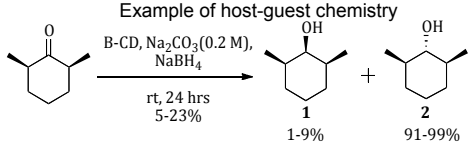
- 2,6-dimethylcyclohexanol was selected for further studies in this project because it has a strong anesthetic potency and is available commercially.
- Due to the chirality of the body, single stereoisomers act differently in environments within the body.
- This compound exists as two diastereomers and a set of enantiomers (box above).
- Testing with cyclohexanol derivatives pictured above used mixtures of isomers.

Reactions

Reduction reactions of 2,6-dimethylcyclohexanone:

1) Reaction with β-cyclodextrin: poor yields after various attempts at optimization

Example of host-guest chemistry

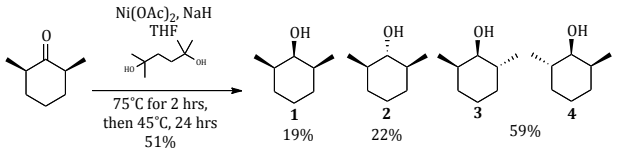


2) Reaction with metal complex reducing agent (MCRA)

Example of aggregate activation

MCRA synthesized from NaH, $Ni(OAc)_2$, and 2,6-dimethyl-2,5-hexanediol

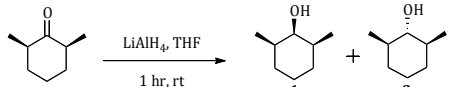
Produced mixtures of isomers that can't be separated by column chromatography

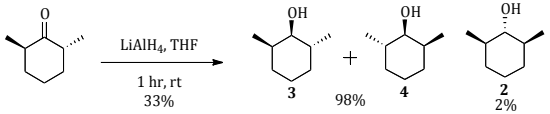


3) Simple Reducing Agents: used to synthesize all isomers

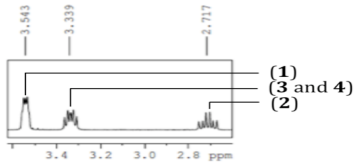
Separation of isomer *1* from *2* using column chromatography

Isomers *3* and *4* left as enantiomeric mixture





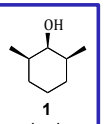
NMR Analysis



Resolution of diastereomers was confirmed with 1D ^{1}H NMR. Unique ^{1}H NMR peaks are represented with isomer assignments.

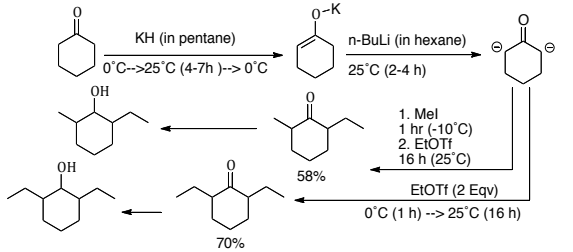
Unlikely Discovery

By using common reducing agents, all isomers could be separated (the mixture of enantiomers were not separated). Further experimentation by the Hall lab revealed *cis,cis*-2,6-dimethylcyclohexanol as the most potent isomer.



Future Approaches

•Synthesize cyclohexanone precursors, asymmetric and symmetric, that likely can be reduced using $LiAlH_4$ with separation of stereoisomers via column chromatography:



•Test individual stereoisomers as potential anesthetics.

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